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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C08F 2/00, G01N 21/00, B01L 3/00, C12C 1/00

A1

(11) International Publication Number: WO 97/09353

(43) International Publication Date: 13 March 1997 (13.03.97)

(21) International Application Number: PCT/US96/14325

(22) International Filing Date: 6 September 1996 (06.09.96)

(30) Priority Data:
08/524,943 7 September 1995 (07.09.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/524,943 (CIP)
Filed on 7 September 1995 (07.09.95)

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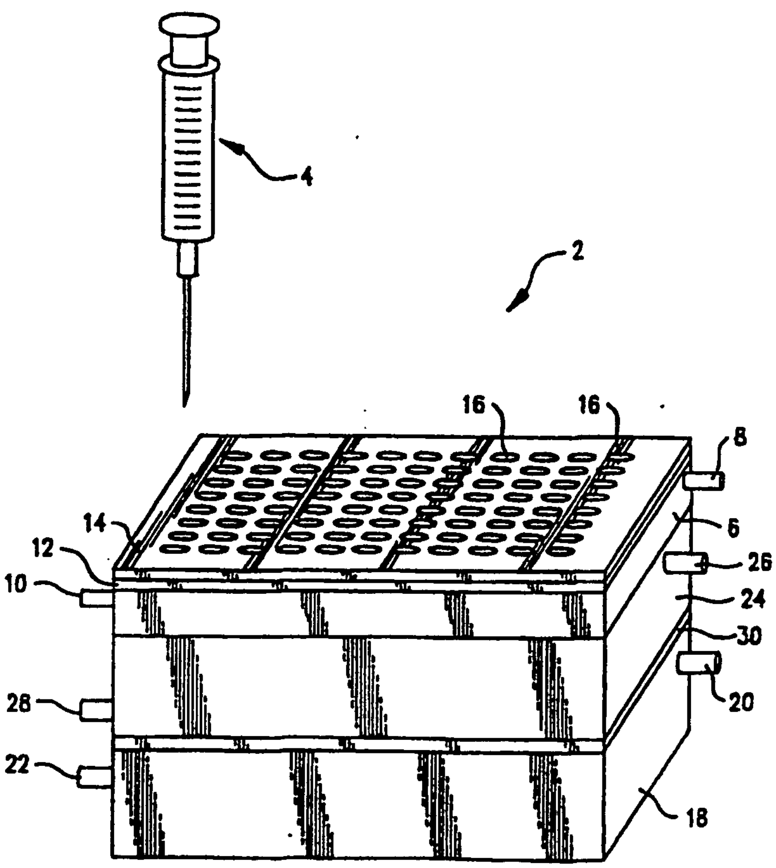
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: A DEVICE FOR THE SYNTHESIS OF COMPOUNDS IN AN ARRAY

(57) Abstract

A method and device (2) for the simultaneous production of chemical compounds in an array which is capable of providing a very broad range of reaction environments including reaction temperatures of -40 °C to 150 °C, reflux condensation, and a selective gas environment. The invention also allows the addition of several reagents (4) during the course of the production process. The device (2) is comprised of a number of different block sections (6, 24, 18) which are fastened together to provide the required reaction environment.



Ref. #36
Dales, et al.
SMX 3104 (2000-108)
09/772,101

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A DEVICE FOR THE SYNTHESIS OF COMPOUNDS IN AN ARRAY

Field of the Invention

The present invention relates to a device and method for the production of chemical compounds. More specifically the device and method relate to the simultaneous production of chemical compounds in an array.

Background of the Invention

Numerous methods and apparatus are well known in the prior art for the multiple simultaneous synthesis of peptides and oligonucleotides. However, all of these methods and devices are limited in one way or another in the range of reaction environments they can provide for or the types of reagents they can accommodate in carrying out a chemical process. Some systems can handle large arrays of reactions and a wide variety of reagents, but only for chemical r actions to be carried out at room temp rature. Other systems can eith r heat or cool an

ongoing r action, but are unable to pr vide a reflux condenser to return a portion of th product stream to the chemical process. And still others ar unable to provide an oxygen free environment within which to carry out the reaction.

One such known methodology is a solid state technique for the synthesis of peptides and oligonucleotides developed by Affymax Technologies N.V. and disclosed in United States Patent No. 5,143,854. The Affymax technique involves sequentially using light to illuminate a plurality of polymer sequences on a substrate and delivering reaction fluids to the substrate. Whil undeniably useful, this system is limited to a small number of reactions and produces only trace amounts of product.

Another method and device for the synthesis of organic compounds is disclosed in Cody et al., United States Patent No. 5,324,483 (Jun. 28, 1994), Apparatus for Multiple Simultaneous Synthesis. The Cody device consists of a reservoir block having a plurality of wells; a plurality of reaction tubes, usually gas dispersion tubes, having filters on their lower end; a holder block, having a plurality of apertures; and a manifold which may have ports to accommodate the maintenance/introduction of a controlled environment. The top wall has apertures and a detachable plate with identical apertures. While an advancement over the prior art, the Cody apparatus does not easily facilitate the heating, cooling, and reflux of the product as does th present invention.

Summary f th Inv ntion

The present inv ntion concerns a method and d vice for the simultaneous synthesis of organic compounds in an array. It provides a very broad range of reaction environments including, but not limited to reaction temperatures of -40°C to 150°C, reflux condensation, a selective gas environment, and addition of several reagents during the course of reaction. The present invention is uniquely suited to auxiliary processes including rotational shaking, magnetic stirring, sonicating, photo chemistry, and robotic automation.

The device of the present invention is most generally referred to as an array synthesis block and is made up of a number of smaller subunits in combination. The various subunits are assembled in a stack depending upon the type of reaction environment required by the desired synthesis. The devic includes a retaining block section for holding reaction vessels. The preferred form of the retaining block section also incorporates gas flow channeling for providing a selective gas atmosphere. Usually nitrogen, argon, or some other inert gas is used in order to carry out reactions to the exclusion of oxygen. One or more temperature control block sections are combined with the retaining block section in order to heat and/or cool the reaction vessels. Heating or cooling is accomplished through the use of electrical heating/cooling elements and/or the circulation of a heating/cooling fluid. A reflux control block section required for certain synthesis is combined with the temperature control block section and th retaining block section in a stack in order to provide reflux cond nsation during r action. Cooling

gas or liquid is circulated through the r flux control block section. Alternatively, a portion of th of the reflux chamber is filled with a solid coolant such as ice or solid CO_2. Thes block sections are fastened together in a stack to form the array synthesis block. Fastening is accomplished by any number of suitable methods such as bolts passing through registering hol s in the multiple block sections, clips holding the multiple block sections together, or an exterior bracket that clamps the block sections together as an assembled synthesis block. Once th individual sections of the synthesis block are fastened together the entire unit can be sonicated or fastened onto a rotational shaker.

Brief Description of the Drawings

The invention, together with further advantages thereof, may best be understood by reference to the following description taken in conjunction with the accompanying drawings in which:

FIG. 1a is an isometric view of one embodiment of an array synthesis block utilizing a retaining block section, a reflux control block section, and a temperature control block section.

FIG. 1b is an enlarged partial cross-section view of a retaining block section illustrating the use of a needle to add reagents to the reaction vessels while maintaining a selective gas environment.

FIG. 2 is an explod d isometric view of FIG. 1a showing an attached reaction v ssel.

FIG. 3a is a top down view of a r taining block section.

FIG. 3b is a partial cross-s ction view of the retaining plate illustrated in FIG. 3a.

FIG. 4a is an isometric view of an alternative embodiment for a retaining block section.

FIG. 4b is a partial cross-section view of an alternative embodiment for a retaining block section.

FIG. 4c is a top down view of an alternative embodiment of a retaining block section.

FIG. 5a is an isometric view of a reflux control block section, a spacer plate, and a temperature control block section of a multiple array synthesis block.

FIG. 5b is an exploded cross-section view of FIG. 5a

FIG. 6 is an exploded isometric view of an alternative embodiment of a multiple array synthesis block utilizing a splash guard and insulator mounted on top of the temperature control block section.

FIG. 7a is a front orthogonal cross-section view of a preferred embodiment of the synthesis block.

FIG. 7b is a side orthogonal cross-section view of the synthesis block in FIG. 7a.

FIG. 7c is a top orthogonal cross-section view of the synthesis block in FIG. 7a.

FIG. 8a is a top orthogonal view of the sealing plate used in the synthesis block in FIG. 7a.

FIG. 8b is a side orthogonal cross-section view of the sealing plate in FIG. 8a.

FIG. 8c is a front orthogonal cross-section vi w of the sealing plate in FIG. 8a.

FIG. 9a is a top orthogonal view of th securing plate used in the synthesis block in FIG. 7a.

FIG. 9b is a side orthogonal cross-section view of the securing plate in FIG. 9a.

FIG. 9c is a front orthogonal cross-section view of the securing plate in FIG. 9a.

FIG. 10a is a top orthogonal view of the retaining block used in the synthesis block in FIG. 7a.

FIG. 10b is a side orthogonal cross-section view of the retaining block in FIG. 10a.

FIG. 10c is a front orthogonal cross-section view of the retaining block in FIG. 10a.

FIG. 11a is a top orthogonal view of the insert retaining plate used in the synthesis block in FIG. 7a.

FIG. 11b is a side orthogonal cross-section view of the insert retaining plate in FIG. 11a.

FIG. 11c is a front orthogonal cross-section view of the insert retaining plate in FIG. 11a.

FIG. 12a is a top orthogonal view of the upper heating and cooling block used in the synthesis block in FIG. 7a.

FIG. 12b is a side orthogonal cross-section view of the upper heating and cooling block in FIG. 12a.

FIG. 12c is a front orthogonal cross-section view of the upper heating and cooling block in FIG. 12a.

FIG. 13a is a top orthogonal vi w of the lower heating and cooling block used in the synthesis block in FIG. 7a.

FIG. 13b is a side orthog nal cross-section view of the lower h ating and cooling block in FIG. 13a.

FIG. 13c is a front rthogonal cross-section vi w of the lower heating and cooling block in FIG. 13a.

FIG. 14a is a top orthogonal view of a room temperature frame for use with the synthesis block in FIG. 7a.

FIG. 14b is a side orthogonal cross-section view of the room temperature frame in FIG. 14a.

FIG. 14c is a front orthogonal cross-section view of the room temperature frame in FIG. 14a.

preferred

Detailed Description of the Invention

Shown in FIG. 1a is the basic multiple array synthesis block 2 and a needle equipped syringe 4. The basic components of the synthesis block 2 are: the retaining block section 6 having a retaining block section gas or liquid inlet 8 and in some embodiments a retaining block section gas or liquid outlet 10, a needle penetrable septum 12, a securing plate 14 having in one embodiment an array of apertures 16, a temperature control block section 18 having a fluid inlet 20 and a fluid outlet 22, a reflux control block section 24 having a condensing coolant inlet 26 and a condensing coolant outlet 28, and a spacer plate 30.

Referring to FIG. 1b, the retaining block section 6 has an array of apertures 38 passing through it. Along the top surface of this block 6 the apertures 38 are covered with a needle p netrable septum 12. This septum 12 is held in place

by a securing plate 14 which has an array of securing plate apertures 16 passing through it and which ar in registration with the apertures 38 in the r taining block secti n 6. Th bottom portion of the apertures 38 in the retaining block section 6 are provided with a securing means 34 for fastening the open ends of the reaction vessels 32. Rubber O-rings 35 are placed in apertures 38 between the open ends of the reaction vessels 32 and the top portion of the apertures 38. Reaction vessels 32 are secured in place by mating threads on the lower interior surfaces of the threaded apertures 38 and the outside of top ends of the reaction vessels 32. The vessels 32 are then secured to the synthesis block 2 by screwing them into the lower portion of the apertures 38 in the retaining block section 6 to a depth in which the O-rings compress and form a tight seal between the top of aperture 38 and reaction vessel 32. Alternatively, a clip mechanism can be used to secure the reaction vessels 32 to the retaining block section 6.

The retaining block section 6 also has a series of gas flow channels 36 running through it which interconnect the apertures 38 above the point at which the reaction vessels 32 are secured. These gas flow channels 36 can be beneath the top surface of the retaining block section 6 or they may simply be routed out the top surface. If the channels 36 are routed out of the top surface, then septum 12 and securing plate 14 serve the dual purposes of enclosing the channels 36 and covering the tops of th ap rtures 38. The retaining block 6 section also has a gas inl t 8 which is generally

connected to a source of gas in order to provide an inert gas environment to the individual vessels 32. Additionally, referring back to FIG 1a, a gas outlet 10 may be provid d in the retaining block section 6. Depending upon the fastening means chosen to hold the multiple array synthesis block 2 together, the securing plate, the septum, and the retaining block section may be provided with a series of aligned fastener holes.

FIG. 2 illustrates how the synthesis block 2 is assembled from the component block sections. The array of securing plate apertures 16, retaining block section apertures 38, and the reflux control block section apertures 40 are all in registration. The securing plate apertures 16 each need only be large enough to accommodate a needle. This figure also clearly illustrates how the septum 12 and securing plate 14 cover the open tops of channels 36 and the tops of the apertures 38 in the retaining block section 6. It can also be seen that the top of the temperature control block section 18 is open and that a fluid receiving cavity 42 is formed on the inside and that the closed bottom end of the reaction vessels 32 extend into the temperature control block section 18. One embodiment of the present invention includes a spacer/insulator plate 30 between the temperature control block section 18 and the reflux control block section 24 as illustrated in FIG. 1a.

FIG. 3a shows how the channels 36 ar laid out in the retaining block section 6 and illustrat s one possibl placement of bolt holes 44 and alignment post hol s 46 us d in

assembling the synthesis block 2. FIG. 3b illustrates one emb diment of how the channels 36 can be c nnected to the retaining block gas inlet 8.

FIG. 4a shows an alternative layout for the channels 36 in retaining block section 6 and includes a retaining block gas outlet 10. FIG. 4c illustrates how the alternative network of channels 36 are connected to the retaining block gas inlet 8 and the retaining block gas outlet 10.

Referring to FIG. 5a the reflux control block section 24, the spacer/insulator plate 30, and the temperature control block section 18 are illustrated. FIG. 5b further illustrates that there is a second set of apertures 48 in the bottom of the reflux control block section 24 and that the spacer/insulator plate 30 also has a set of apertures 52 passing through it. A series of rubber O-rings 50 are used to form a seal between temperature control block section 18 and the reflux control block section 24. The bottom edges of apertures 48 and the upper edges of apertures 52 are bevelled to increase the efficacy of the O-rings 50.

FIG. 6 shows an alternate embodiment including spacer/insulator plate 30 and splash guard 54. Splash guard 54 is comprised of three subunits: a splash guard top piece 51, a rubber splash guard gasket 53, and a splash guard base plate 55. All three subunits have an array of apertures in registration with each other and the apertures in spacer/insulator plate 30. The apertures in splash guard gasket 53 are slightly smaller in diameter than th apertur s in the splash guard top piece 51 and th splash guard base

plat 55 so as t provid a tight seal ar und reaction v ssels.

Construction and Materials

The basic components of the synthesis block 2 can be constructed out of any number of well known materials. The only restrictions are that they must be able to withstand the operating temperatures of the device and not react with the reagents and gasses to which the components will be exposed. The retaining block section 6 is preferably made out of Teflon™, but could alternatively be made from plastic, ceramic or other non-reactive material. In one embodiment the retaining block section 6 is a relatively flat panel having exterior dimensions of 12"x13"x1/2". The needle penetrable septum 12 is preferably made out of a sheet of silicon rubber, but another type of elastomeric polymer could easily be substituted. In one embodiment the needle penetrable septum 12 has the dimensions of 12"x13"x1/8". The securing plate 14 is preferably made out of aluminum, but could alternatively be made from plastic, ceramic, Teflon™, or another suitable metal. In one embodiment the securing plate 14 has the dimensions of 12"x13"x1/2". The temperature control block section 18 is preferably made out of aluminum, but could alternatively be made from another metal, plastic, or ceramic. In one embodiment the temperature control block section 18 has the dimensions of 12"x13"x2.5". The reflux control block section 24 is preferably made out of aluminum, but could alternatively b made from plastic, m tal, ceramic, or glass.

In one embodiment the reflux c ntrol block section 24 has the dimensions of 12"x13"x2.125". Th spacer/insulator plate 30 is preferably made out of Tefl n™, but could alt rnatively be made from plastic, ceramic, or metal. In one embodiment the spacer/insulator plate 30 has the dimensions of 12"x13"x1/4". The splash guard 54 has dimensions roughly approximate to those of other components of the device and its top piece 51 and splash guard base plate 55 are preferably made of aluminum, but could alternatively be made from plastic, ceramic, or some other metal. The reaction vessels 32 are preferably made of glass, but other nonreactive materials could be used including plastic. The reaction vessels come in two sizes with the large vessels measuring approximately 16mm in diameter and 125mm in length and the small vessels measuring approximately 16mm in diameter and 60mm in length. The larger tubes are used primarily when reflux condensation is called for and the additional length is required to accommodated the reflux control block section 24 and provide additional volume for condensation to form.

<u>Assembly of the Generalized Embodiment</u>

The retaining block section 6, septum 12, and securing plate 14 are assembled as shown in FIG. 1b using 12 bolts, 8 bolts evenly spaced around the perimeter of Plate 14 and 4 bolts evenly around the center of plate 14. Rubber O-rings are place in each aperture 38 so as to rest against the top of the threaded section. Individual reaction vessels 32 with thr ad d tops are screwed into apertur s 38. The entire

reaction block assembly (retaining bl ck section 6, septum 12, securing plat 14, and r action vessels 32) is attached to th temperature control block section 18 ither directly or in combination with the reflux control block section 24 as shown in FIG. 2. An inert gas hose is connected to the reaction block section 6 using gas inlet port 8. Cooling water inlet and outlet hoses (if applicable) are connected to the reflux block section 24 via condensing coolant inlet 26 and condensing coolant outlet 28. Heating and cooling hoses are attached to the temperature control block section 18 using fluid inlet 20 and fluid outlet 22. The assembled device is placed on an orbital shaker such as the Bohdan Labline orbital shaker (Mundelein, Illinois) for stirring agitation. Inert gas, cooling water (if applicable), and heating or cooling fluid at the desired temperature is applied to the device. The device is now ready to receive solvents, chemical reagents and substrates.

Operation of the Generalized Embodiment

The individual reaction vessels 32 are purged with inert gas by inserting a hollow open ended needle through the septum 12 into each reaction vessel 12. Air is removed from the vessel 32 by closing gas outlet 10 and creating a vacuum at gas inlet 8. After the air is removed the vessel 32 is filled with an inert gas such as argon through gas inlet 8.

The next operational step involves the sequential introduction of solvents, chemical reagents, and substrates into the vessels 32 via syringe needle 4.

After the solvents, chemical reagents, and substrates are combined, th orbit shak r is turned on and an appropriate agitation level is sel cted to insure an even and c ntrolled mixing of the reaction vessel contents. When the reactions are completed, the reaction vessels 32 brought to room temperature, water is added to the vessels and the desired reaction products are isolated by organic solvent extraction.

Description of the Embodiment Disclosed in Figures 7-14

FIGS. 7a, 7b, and 7c illustrate the preferred embodiment of the inventive reaction synthesis block 2 sitting inside insulating sleave 3a which is further comprised of insulating sleave liner 3b and insulating sleave base 3c.

Synthesis block 2 is comprised of the retaining block section 6 having at least one reaction vessel securing insert 7, an insert retaining plate 9, a retaining block section gas inlet 8 and a retaining block section gas outlet 10, a needle penetrable septum 12, a securing plate 14 having an array of securing plate apertures 16, an upper temperature control block section 18a having a fluid inlet 20a and a fluid outlet 22a, a lower temperature control block section 18b having a fluid inlet 20b and a fluid outlet 22b, upper insulating plate 23a, lower insulating plate 23b.

FIG. 8 illustrates that synthesis block 2 may also include a securing plate 5a and a securing septum 5b. Securing plate 5a is preferably manufactured from aluminum and securing septum 5b is pr ferably manufactured from a Teflon coated silicon rubber such as 45 Durometer.

FIGS. 9a, 9b, and 9c illustrate s curing plate 14 and securing plate apertur s 16. Securing plat 14 is pr ferably constructed out of aluminum. The needle penetrable septum 12 which is held in place by securing plate 14 is preferably manufactured from a Teflon coated silicon rubber such as 45 Durometer.

FIGS. 10a, 10b, and 10c show retaining block section 6 having an array of apertures 38 into which the reaction vessel securing inserts 7 are fitted. Retaining block section 6 is preferably manufactured from Fluorosint 500. The reaction vessel securing inserts 7 have a larger diameter than the diameter at the top of the retaining block apertures 38. The reaction vessel securing inserts 7 have apertures which are in registration with the array of apertures 38 in retaining block section 6. The reaction vessel securing inserts 7 use form fitted Teflon coated O-rings to seal the reaction vessel and external Teflon coated O-ring to seal to the Flourosint 500 retaining block section 6. A mounting pin is used to prevent rotational slippage and is fitted into the groove in the retaining block apertures 38.

The insert retaining plate 9 is illustrated in FIGS. 11a, 11b, and 11c. Insert retaining plate 9 has a plurality of apertures 11 which are in registration with the array of apertures 38 in the retaining block section 6 and the apertures in the reaction vessel securing inserts 7. Insert retaining plate 9 is preferably manufactured from aluminum.

FIGS. 12a, 12b, and 12c show upper temperature control block section 18a having a fluid inlet 20a and a fluid outlet

22a, a plurality of temperature control block apertures 19a, h ating elem nt cavities 21a, heating el ments 21b, temperature sensor cavities 23a, and temperature sensors 23b. Upper temperature control block section 18a is also provided with a series of fluid circulating conduits 25a in communication with fluid inlet 20a and fluid outlet 22a. The reaction block 2 is cooled by circulating cooling fluids through the fluid circulating conduits 25a by means of a pump via fluid inlet 20a and fluid outlet 22a.

Figs 13a, 13b, and 13c, show a lower temperature control block section 18b having a fluid inlet 20b and a fluid outlet 22b, a plurality of temperature control block round bottomed cylindrical indentations 19b, heating element cavities 21a, heating elements 21b, temperature sensor cavities 23a, and temperature sensors 23b. Lower temperature control block section 18b is also provided with a series of fluid circulating conduits 25b in communication with fluid inlet 20b and fluid outlet 22b. The reaction block 2 is cooled by circulating cooling fluids through the fluid circulating conduits 25b by means of a pump via fluid inlet 20b and fluid outlet 22b.

The heating elements, pump/pumps connected to the fluid inlets and outlets, and the temperature sensors in the upper and lower temperature control blocks 18a and 18b can be connected to an electrical control circuit which maintains pr programmed t mperatures in the upper and lower temperature control blocks 18a and 18b.

Upper insulating plate **23a** and lower insulating plate **23b** ar both pr ferably manufactur d from Fluorosint 500. Upper insulating plat **23a** is also provided with a series of apertures through which reaction vessels **32** pass through and depend from into the lower temperature control block section **18b**.

FIGS. **14a**, **14b**, and **14c** illustrate the airframe **56** which is comprised of an upper plate **58** provided with aperature **60** and lip **62**, a plurality of supports **64**, and a base plate **66**. Airframe **56** is used to hold reaction block **2** while carrying out reactions at room temperature or for demonstration purposes.

From the foregoing teachings, it can be appreciated by one skilled in the art that a new, novel, and nonobvious method and device for the simultaneous production of chemical compounds in an array has been disclosed. It is to be understood that numerous alternatives and equivalents will be apparent to those of ordinary skill in the art, given the teachings herein, such that the present invention is not to be limited by the foregoing description but only by the appended claims.

We claim:

1. A d vic for the ret ntion of r action v ssels and th synthesis of compounds in an array comprising:

a) a retaining block section having a top surface and a bottom surface and a plurality of apertures communicating between the top surface and the bottom surface of the retaining block section; and

b) a fastener adapted for securing said reaction vessels within said retaining block section so that openings in said reaction vessels communicate with an associated aperture and closed vessel ends depend downward therefrom.

2. The device of claim 1, wherein said retaining block section is provided with a series of channels interconnecting the apertures in the retaining block section above the point at which the reaction vessel is secured.

3. The device of claim 2, wherein said retaining block has a gas inlet connected to said series of channels.

4. The device of claim 3, wherein said device additionally comprises:

c) a solid needle penetrable septum covering the apertures in the top surface of said retention block section above the point at which the chann ls interconn ct the apertures.

5. The device of claim 4, wherein said devic additionally comprises:

d) a securing plate disp sed above said solid septum and detachably fastening the septum to the top surface of said retention block section , said securing plate having at least one opening in registration with said apertures in the top surface of said retention block section for receiving a needle.

6. The device of claim 5, wherein said device additionally comprises:

e) a temperature control block section having an outer surface, an inner surface, an open top end, and a closed bottom end defining a fluid receiving cavity, said temperature control block section mounted below said retaining block section and receiving said reaction vessels through said open top end so that the downwardly depending closed vessel ends extend below the plane of the open top end and into the fluid receiving cavity.

7. The device of claim 6, wherein said temperature control block section is provided with a fluid inlet and a fluid outlet communicating from the exterior of said temperature control block section and said interior cavity.

8. The device of claim 7, wherein said device additionally comprises:

f) a reflux control block section detachably mounted between said retaining block section and said temperature control block section.

9. The device of claim 8, wherein said reflux control block section is a structure having a top surface and a bottom surface, the structure is formed to provide an interior cavity, and a plurality of apertures are provided to receive a midbody portion of said reaction vessels, between said open upper end and said closed lower end, through the top of said reflux control block section and to allow the bottom ends of said reaction vessels to extend through the bottom surface of said reflux control block section and into said temperature control block section.

10. A device for the retention of a reaction vessel and the synthesis of compounds in an array comprising:

a) a retaining structure having an outside surface defining an interior cavity having an interior surface;

b) a reaction vessel securing structure provided with an aperture in communication with said interior cavity and having a mounting structure for holding the open end of a r action vess l in communication with said interior cavity;

c) a gas inlet port in communication with said interior cavity; and

d) a chemical injection and withdrawal port in communication with said interior cavity and covered with a solid needle penetrable septum and oriented to accommodate the deposition and withdrawal of material from said reaction vessel.

11. The device of claim 10, wherein said device additionally comprises:

e) a second retaining structure having outside surface defining a second interior cavity having an interior surface;

f) a second reaction vessel securing structure provided with a second aperture in communication with said second interior cavity and having a second mounting structure for holding the open end of a second reaction vessel in communication with said second interior cavity;

g) a second gas inlet port in communication with said second interior cavity; and

h) a second chemical injection and withdrawal port in communication with said second interior cavity and covered with a second solid needle penetrable septum and oriented to accommodate the deposition and withdrawal of material from said reaction vessel.

12. Th device of claim 11, wher in said gas inl t port and said second gas inlet port are in communication.

13. Th device of claim 12, wh rein said gas inlet port and said second gas inlet port ar connected to a common sourc of inert gas.

14. The device of claim 13, wherein said chemical injection and withdrawal port and said second chemical injection and withdrawal port are covered with a single solid needle penetrable septum.

15. A method for synthesizing compounds in an array of reaction vessels comprising the steps of:

a) securing from the top an array of reaction vessels having open tops, midbody portions, and closed bottoms;

b) covering the open top of said reaction vessels with a solid needle penetrable septum;

c) flowing inert gas into said reaction vessels in a volume at a pressure sufficient to displace any air present in said reaction vessel;

d) controlling the temperature of the reaction vessels by suspending the bottom end of said reaction vessels in a liquid heating and cooling bath; and

e) depositing reagents necessary to a given synthesis in said reaction vessels through the use of a needle.

16. Th method described in claim 15, wherein the step of controlling the t mperatur of the reacti n vessels is additionally comprised of th substep of suspending said midbody portions of said reaction vessels in a gas cooling unit mounted above said liquid heating and cooling bath.

17. The device of claim 5, wherein said device additionally comprises:

a sealing plate disposed above and detachably fastened to said securing plate so as to substantially close off at least one aperature in said securing plate.

18. The device of claim 17, wherein said device additionally comprises:

a sealing septum disposed between said sealing plate and said securing plate and detachably fastened to said sealing plate and said securing plate so as to substantially close off at least one aperature in said securing plate.

19. The device of claim 5, wherein said device additionally comprises:

an air frame having an upper plate that has an aperature through which said retaining plate is passed and is detachably secured to said air frame and at least one support member having a length greater than the l ng st reaction vessel depending from said retaining plate.

20. The device of claim 19, wh rein said supp rt has at least one ap rature, whereby air may circulate around any dep nding reaction vessels.

21. The device of claim 7, wherein said temperature control block is additionally comprised at least one heating element.

22. The device of claim 21, wherein said heating element is an electrical heating element.

23. The device of claim 22, wherein said temperature control block is additionally comprised at least one temperature sensing element.

24. The device of claim 23, wherein said temperature sensing element is an electrical temperature sensing element.

25. The device of claim 7, wherein said device additionally comprising:

an insulating sleave having a base plate and sidewalls formed to provide an interior cavity into which said reaction block may be securely received and removed and having apertures in registration with said gas inlet and outlet ports and said fluid inlets and outlets.

26. The device of claim 25, wherein said sidewalls are manufactur d from a combination of Rohacell and Flourosint 500.

27. A device for the retention of r action vessels and the synthesis of c mpounds in an array comprising:

a retention block having a top surface, a bottom surface, a plurality of apertures between said top surface and said bottom surface in communication with each other through a series of channels in the top surface of said retention block;

at least one reaction vessel securing insert detachably fastened within one of the apertures in said retention block and provided with an aperture in registration with the aperature within which the reaction vessel securing insert is fastened and having a mounting structure for holding the open end of a reaction vessel in communication with said aperature of said retention block;

a gas inlet port in communication with said series of channels;

a gas outlet port in communication with said series of channels;

an insert retaining plate having a plurality of apertures in registration with the apertures in said retention block and the at least one reaction vessel securing insert, wherein the apertures in said insert retaining plate have smaller diameter than the at least one reaction vessel securing insert;

a solid needle penetrable s ptum covering the apertures in the top surface of said retention block

abov the point at which th channels interc nnect the apertures; and

a s curing plat disposed above said solid needle penetrable septum and detachably fastening the septum to the top surface of said retention block, said securing plate having at least one aperature in registration with said apertures in the top surface of said retention block for receiving a needle.

28. The device of claim 27, wherein said device additionally comprises:

a sealing plate disposed above and detachably fastened to said securing plate so as to substantially close off at least one aperature in said securing plate.

29. The device of claim 28, wherein said device additionally comprises:

a sealing septum disposed between said sealing plate and said securing plate and detachably fastened to said sealing plate and said securing plate so as to substantially close off at least one aperature in said securing plate.

30. A device for the retention of reaction vessels and the synthesis of compounds in an array comprising:

an upper temperature control block having a top surface, a bottom surface, a plurality of apertur s between said top surface and said bottom surface for

r ceiving reaction vessels, and a series of int rc nn cted fluid circulating conduits;

a heating element disposed within said upper temperature control block;

an upper temperature control block fluid inlet in communication with said fluid circulating conduits; and

an upper temperature control block fluid outlet in communication with said fluid circulating conduits.

31. The device of claim 30, wherein said heating element is an electrical heating element.

32. The device of claim 31, wherein said device additionally comprises:

a temperature sensor disposed within said upper temperature control block.

33. The device of claim 32, wherein said temperature sensor is an electrical temperature sensor.

34. The device of claim 32, wherein said device additionally comprises:

a lower temperature control block having a top surface, a bottom surface, a plurality of cylindrical depressions in the top surface for receiving reaction vessels depending from said upper temp rature control block, and a series of interconnected fluid circulating conduits;

a heating element disposed within said upper temperatur control block;

a lower temperature control block fluid inlet in communication with said fluid circulating conduits; and

a lower temperature control block fluid outlet in communication with said fluid circulating conduits.

35. The device of claim 34, wherein said heating element is an electrical heating element.

36. The device of claim 35, wherein said device additionally comprises:

a temeperature sensor disposed within said upper temperature control block.

37. The device of claim 32, wherein said temperature sensor is an electrical temperature sensor.

38. The device of claim 37, wherein said device additionally comprises:

an upper insulating plate, disposed between said upper temperature control block and said lower temperature control block, having a plurality of apertures in registration with the apertures in said upper temperature control block and the cylindrical depressions in said lower temperature control block.

39. A device for the ret ntion of reacti n vessels and the synthesis of compounds in an array comprising:

a retention block having a top surface, a bott m surface, a plurality of apertures between said top surface and said bottom surface in communication with each other through a series of channels in the top surface of said retention block;

at least one reaction vessel securing insert detachably fastened within one of the apertures in said retention block and provided with an aperture in registration with the aperature within which the reaction vessel securing insert is fastened and having a mounting structure for holding the open end of a reaction vessel in communication with said aperature of said retention block;

a gas inlet port in communication with said series of channels;

a gas outlet port in communication with said series of channels;

an insert retaining plate having a plurality of apertures in registration with the apertures in said retention block and the at least one said reaction vessel securing insert, wherein the apertures in said insert retaining plate have smaller diameter than at least one reaction vessel securing insert;

a solid needle penetrable septum covering the apertures in the top surfac of said retention block

abov the point at which the channels int rconnect the apertures; and

a securing plate disposed above said solid needle penetrable septum and detachably fastening the septum to the top surface of said retention block, said securing plate having at least one aperature in registration with said apertures in the top surface of said retention block for receiving a needle.

an upper temperature control block below said insert retaining plate and having a top surface, a bottom surface, a plurality of apertures between said top surface and said bottom surface for receiving reaction vessels depending through apertures in the insert retaining plate, and a series of interconnected fluid circulating conduits;

an electrical heating element disposed within said upper temperature control block;

a fluid inlet in communication with said fluid circulating conduits; and

a fluid outlet in communication with said fluid circulating conduits.

an electrical temeperature sensor disposed within said upper temperature control block.

lower temperature control block below said upper temperature control block and having a top surface, a bottom surface, a plurality of cylindrical depressions in the top surfac for r ceiving reaction vessels d pending

from said upper temp ratur control block, and a series of int rconnected fluid circulating conduits;

an electrical heating element dispos d within said lower temperature control block;

a lower temperature control block fluid inlet in communication with said fluid circulating conduits; and

a lower temperature control block fluid outlet in communication with said fluid circulating conduits.

an electrical temeperature sensor disposed within said lower temperature control block.

an upper insulating plate, disposed between said upper temperature control block and said lower temperature control block, having a plurality of apertures in registration with the apertures in said upper temperature control block and the cylindrical depressions in said lower temperature control block.

40. The device of claim 39, wherein said device additionally comprises:

an insulating sleave having a base plate and sidewalls formed to provide an interior cavity into which said reaction block may be securely received and removed and having apertures in registration with said gas inlet and outlet ports and said fluid inlets and outlets.

41. The device of claim 40, wherein said sidewalls are manufactured from a combination of Rohacell and Flourosint 500.

42. The devic of claim 41, wh rein said devic additionally comprises:

a lower insulating plate disposed between the bottom surface of said lower temperature control block and said base plate.

43. The device of claim 42, wherein said lower insulating plate is manufactured from Flourosint 500.

44. The device of claim 39, wherein said device additionally comprises:

a sealing plate disposed above and detachably fastened to said securing plate so as to substantially close off at least one aperature in said securing plate.

45. The device of claim 44, wherein said device additionally comprises:

a sealing septum disposed between said sealing plate and said securing plate and detachably fastened to said sealing plate and said securing plate so as to substantially close off at least one aperature in said securing plate.

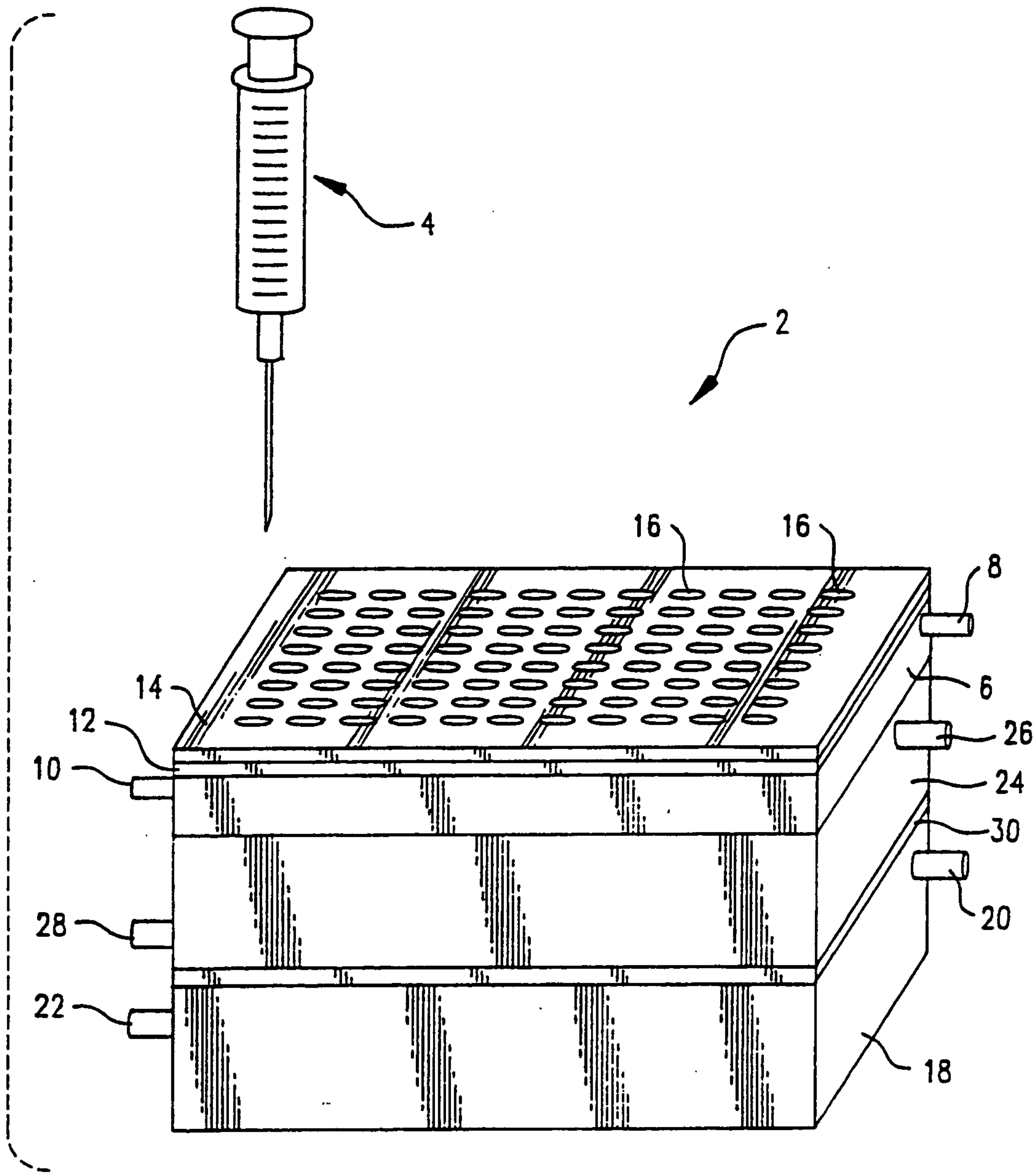
46. The device of claim 39, wherein said device additionally comprises:

an air frame having an upper plate that has an aperature through which said retaining plate is pass d and is detachably s cured to said air frame and at least

on support member having a length gr ater than the longest r action vessel d pending fr m said retaining plate.

47. The device of claim 46, wherein said support has at least one aperature, whereby air may circulate around any depending reaction vessels.

FIG. 1a



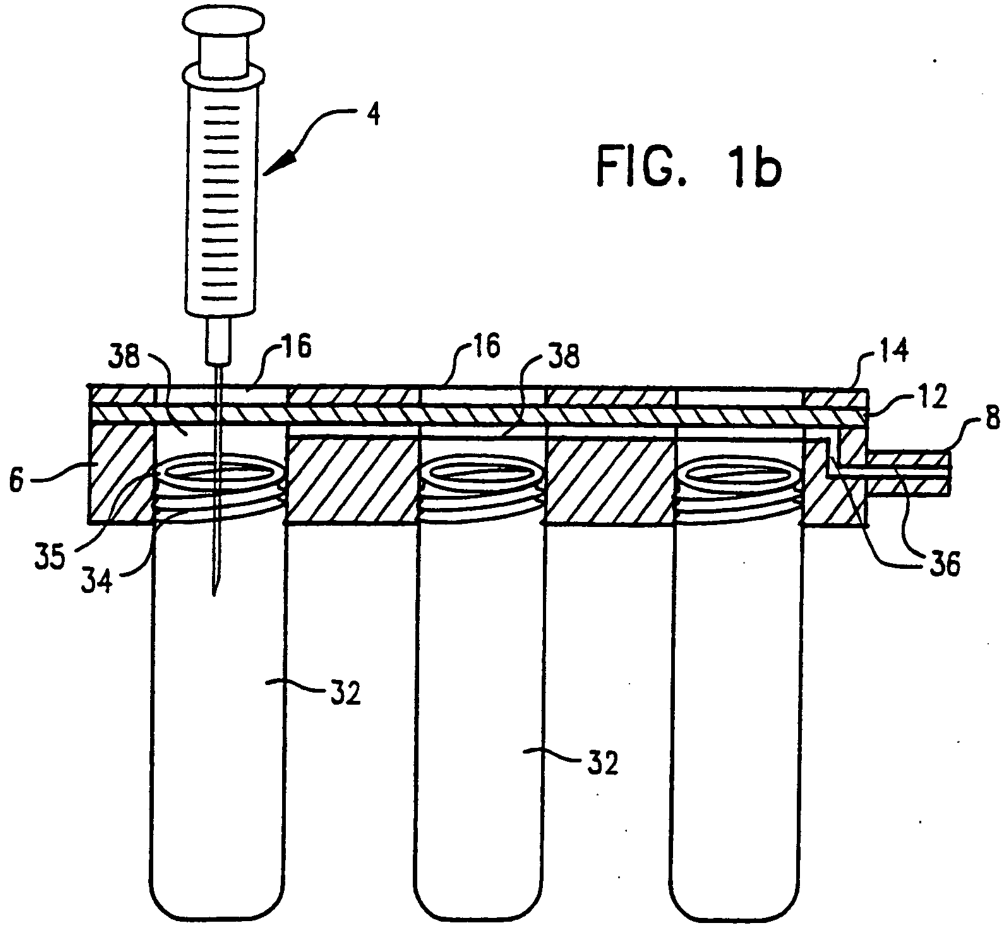


FIG. 1b

FIG. 3a

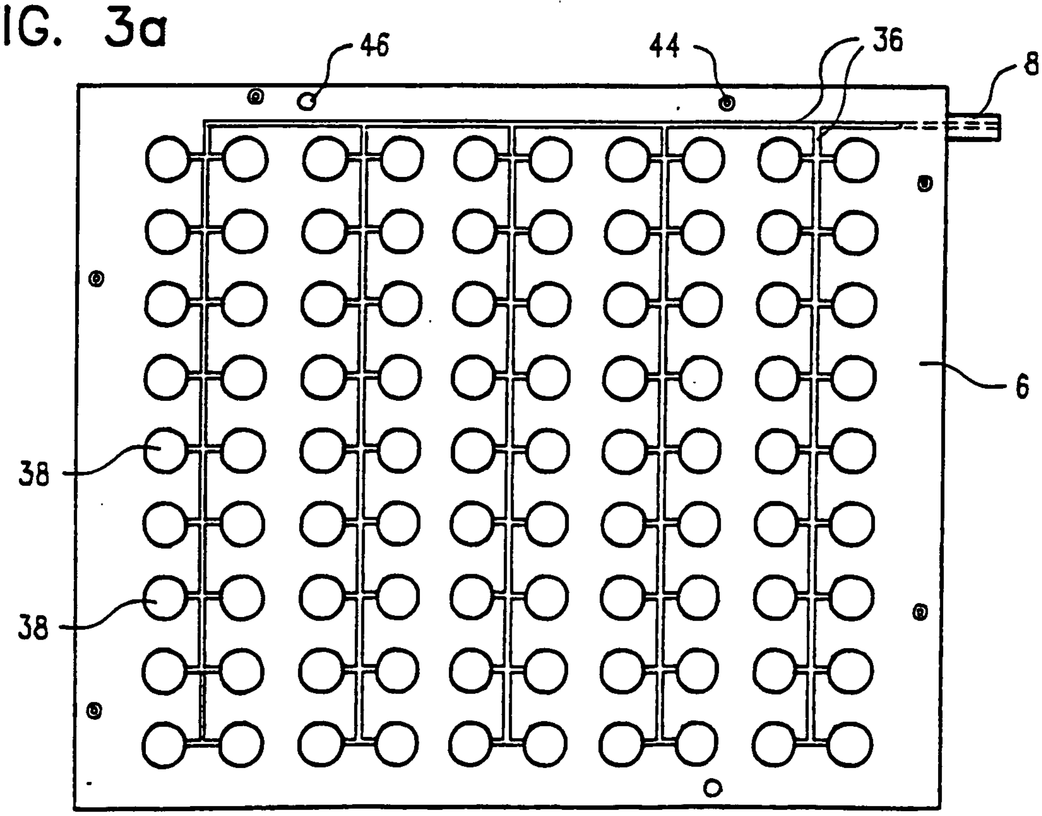


FIG. 2

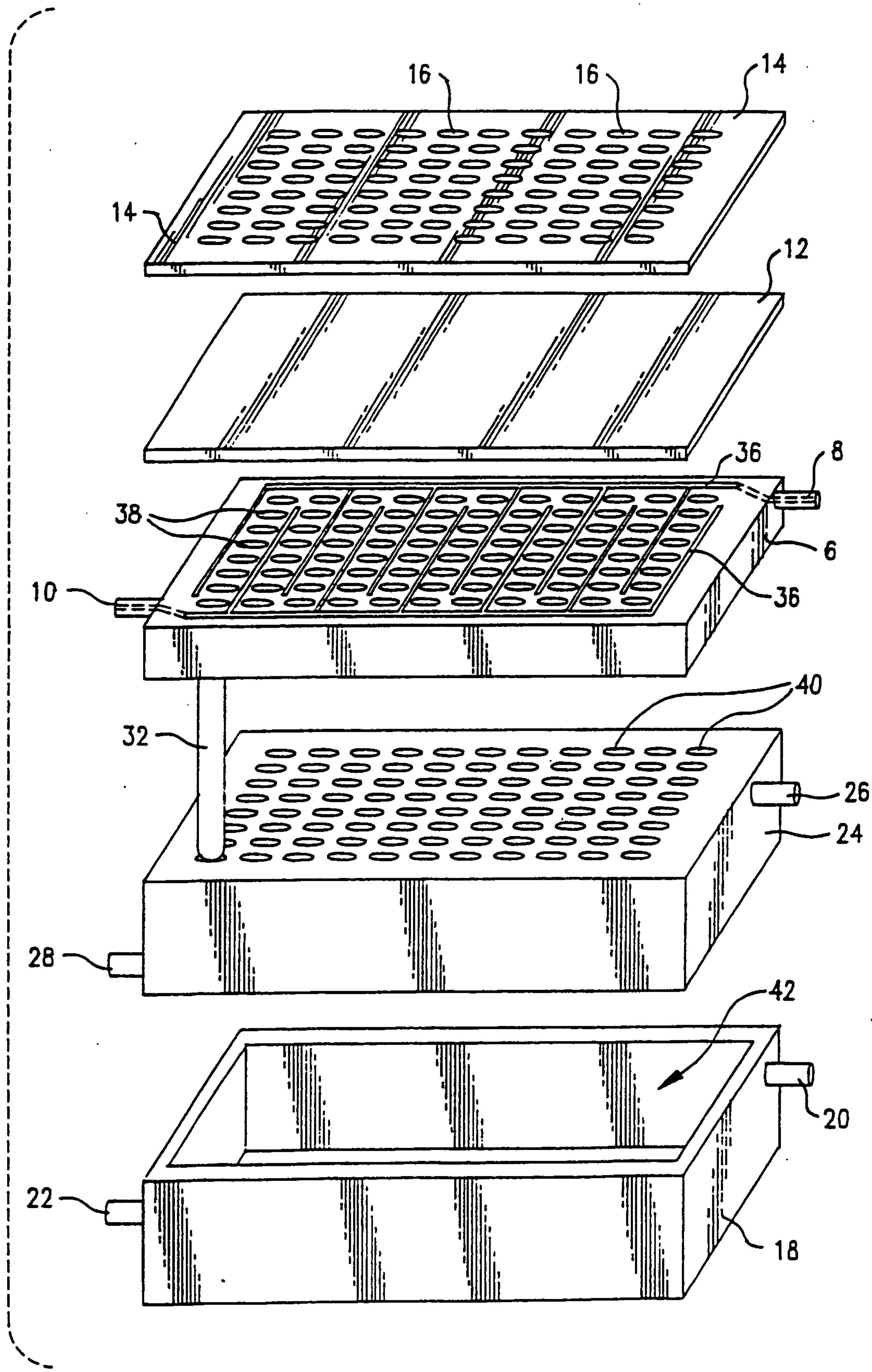


FIG. 3b

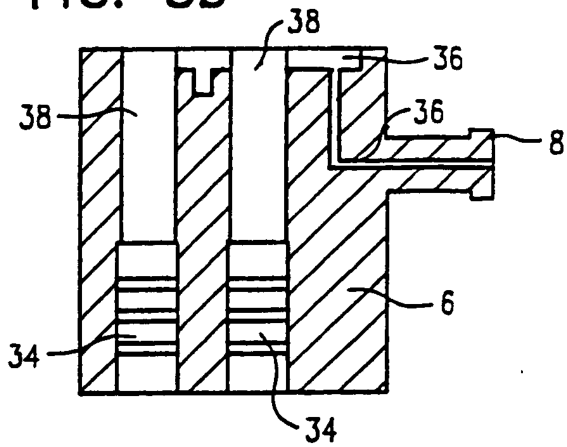


FIG. 4a

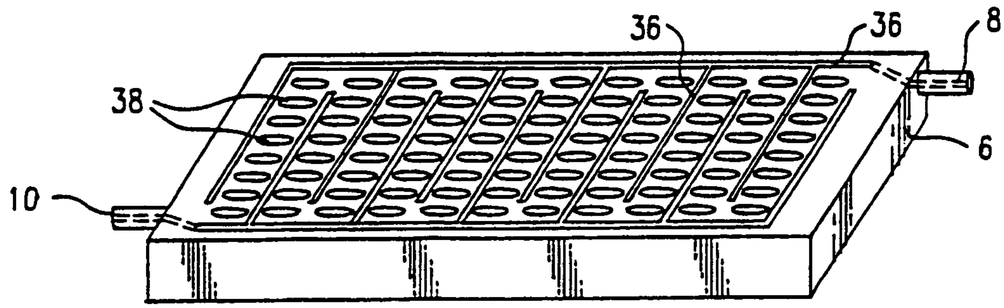


FIG. 4b

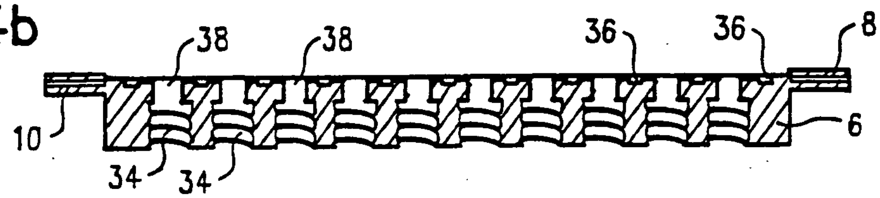


FIG. 4c

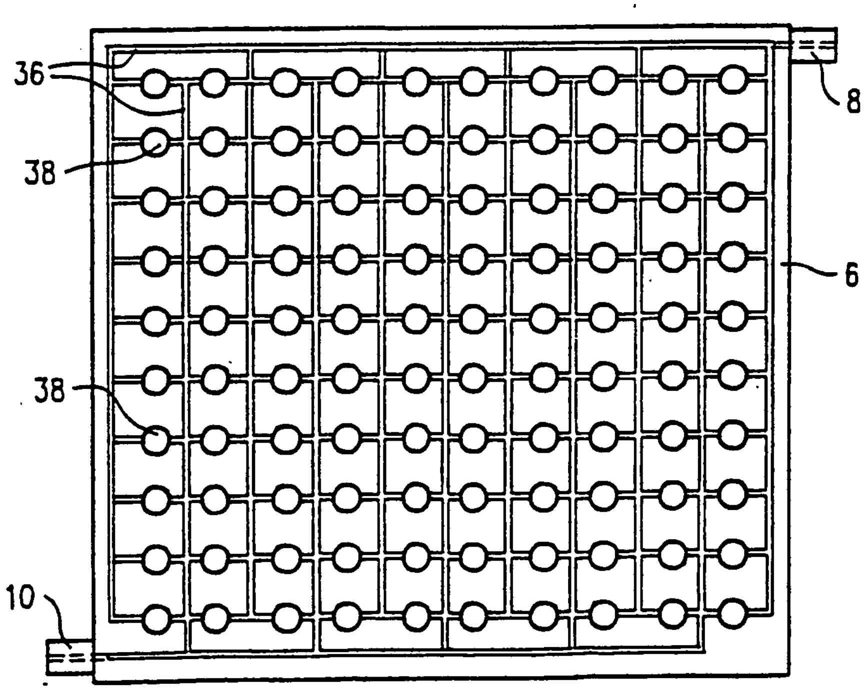


FIG. 5a

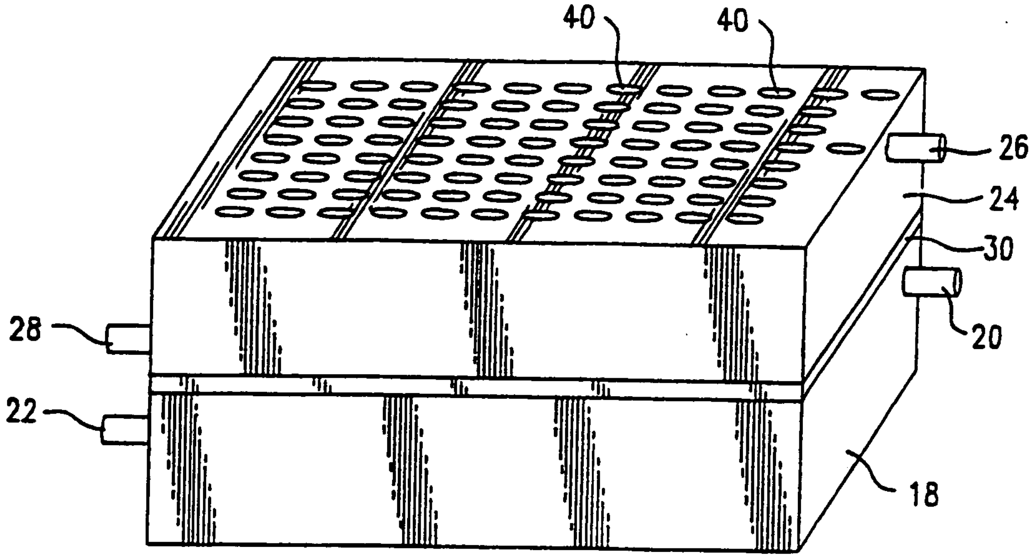


FIG. 5b

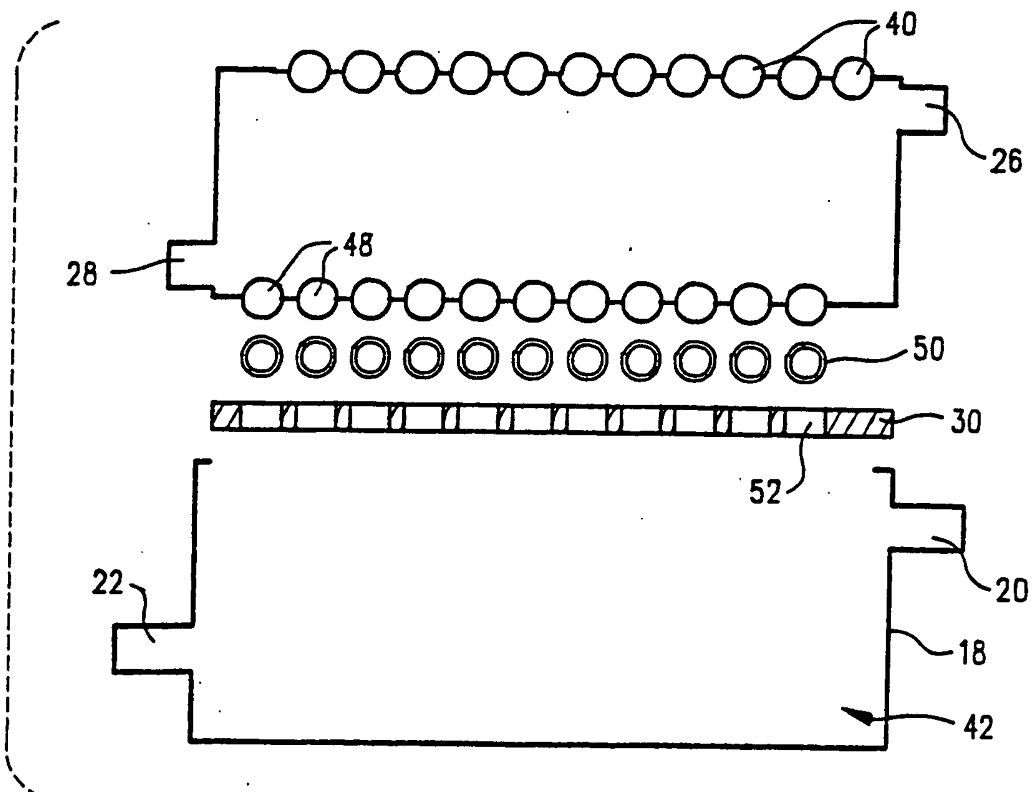


FIG. 6

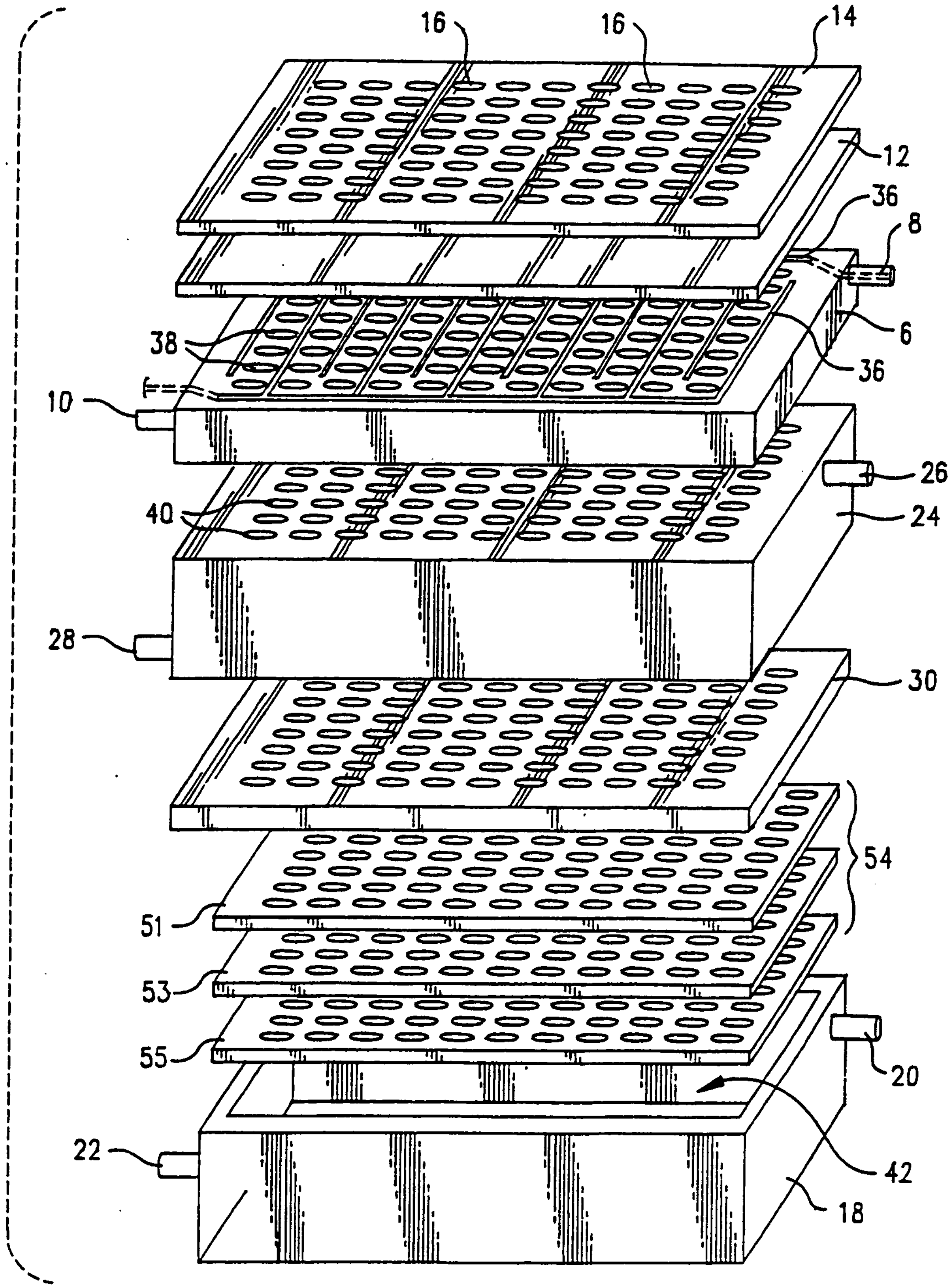
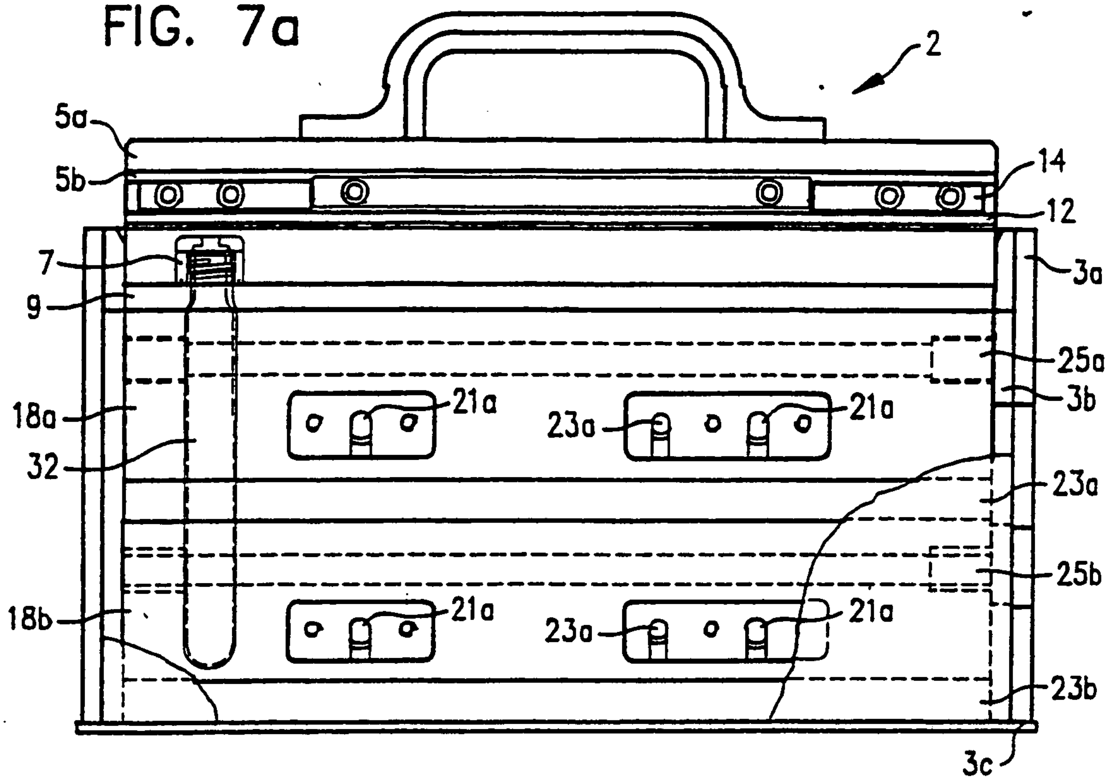


FIG. 7a


2
5a
5b
14
12
7
9
3a
25a
3b
18a
21a
21a
23a
32
23a
25b
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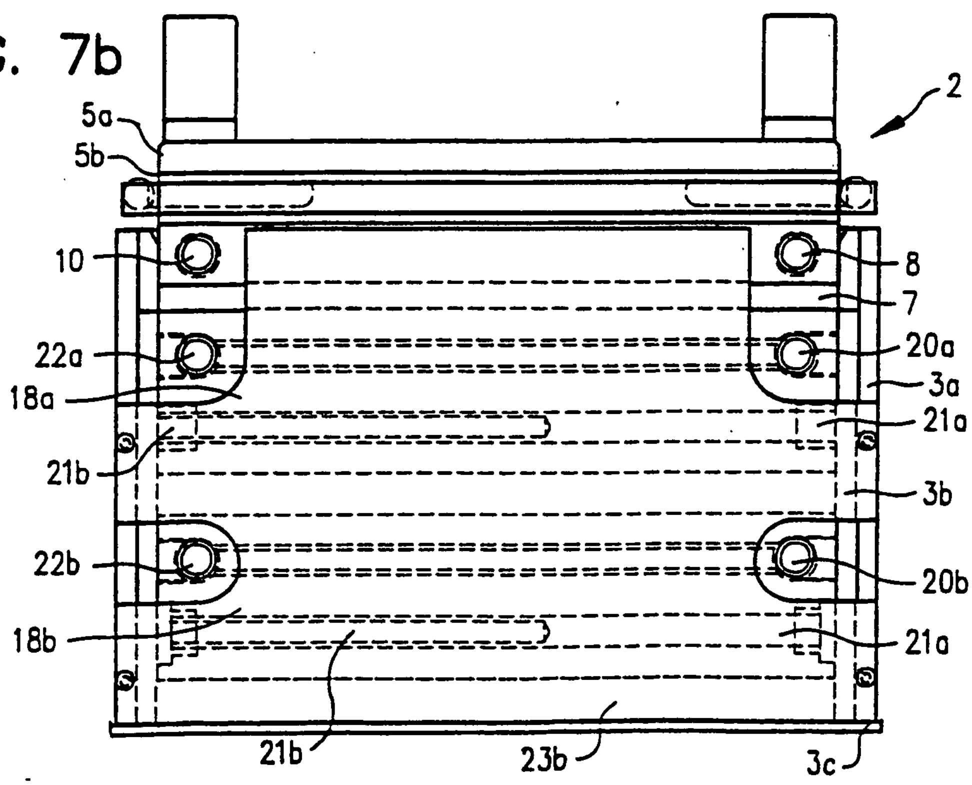
21a
23a
21a
23b
3c

FIG. 7b


2
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5b
10
8
7
22a
20a
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21a
21b
3b
22b
20b
18b
21a
21b
23b
3c

FIG. 7c

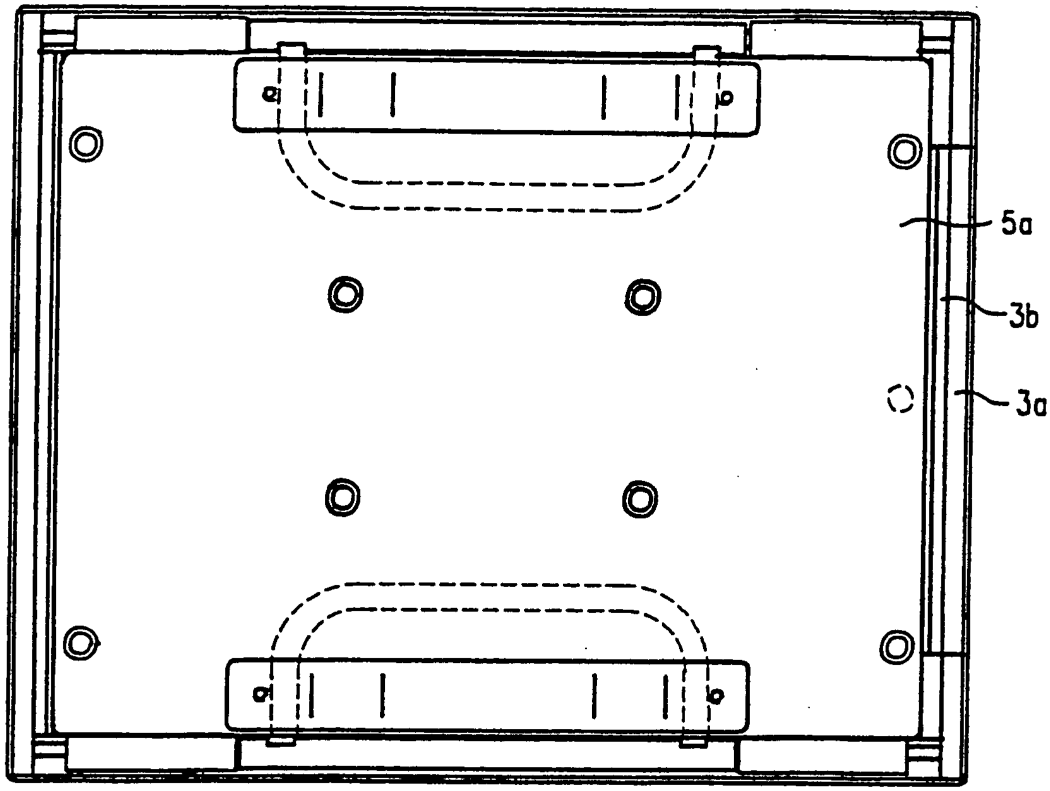


FIG. 8a

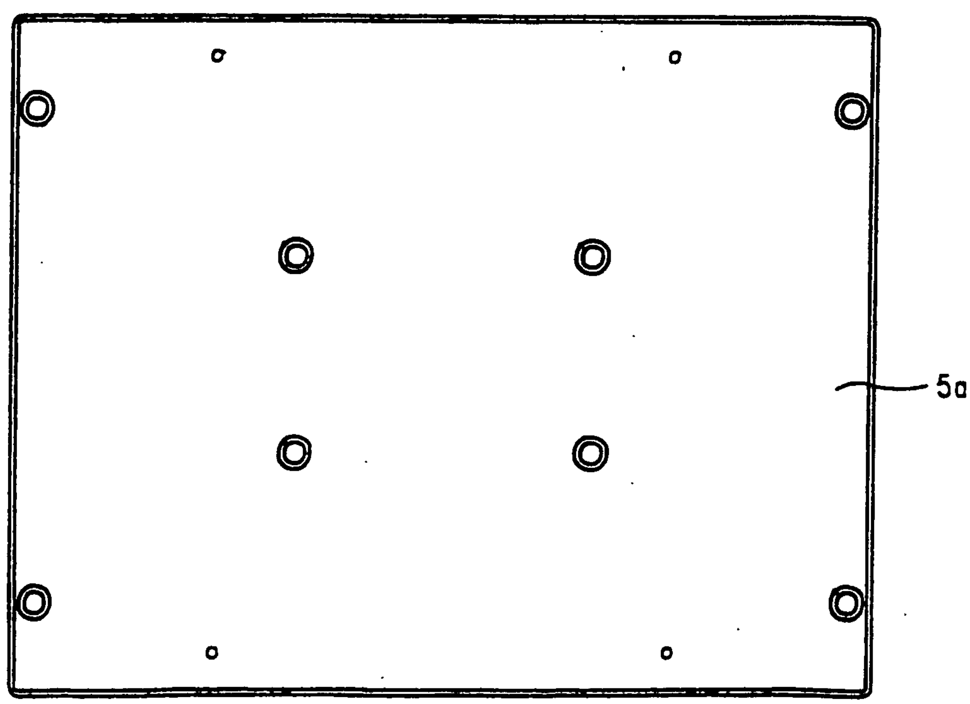


FIG. 8b

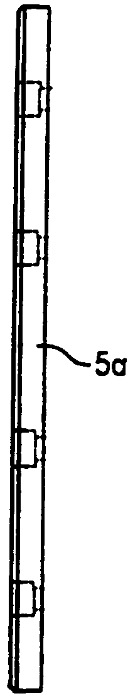


FIG. 8c

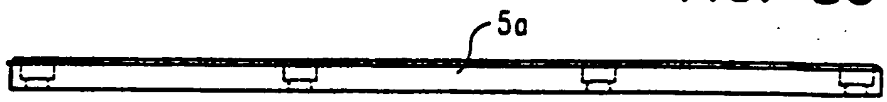


FIG. 9b

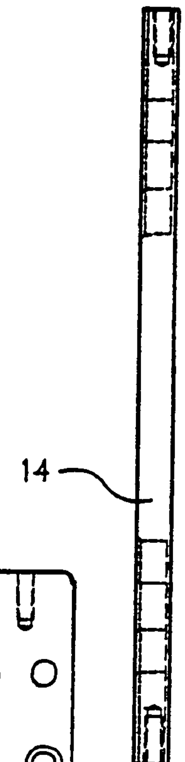


FIG. 9a

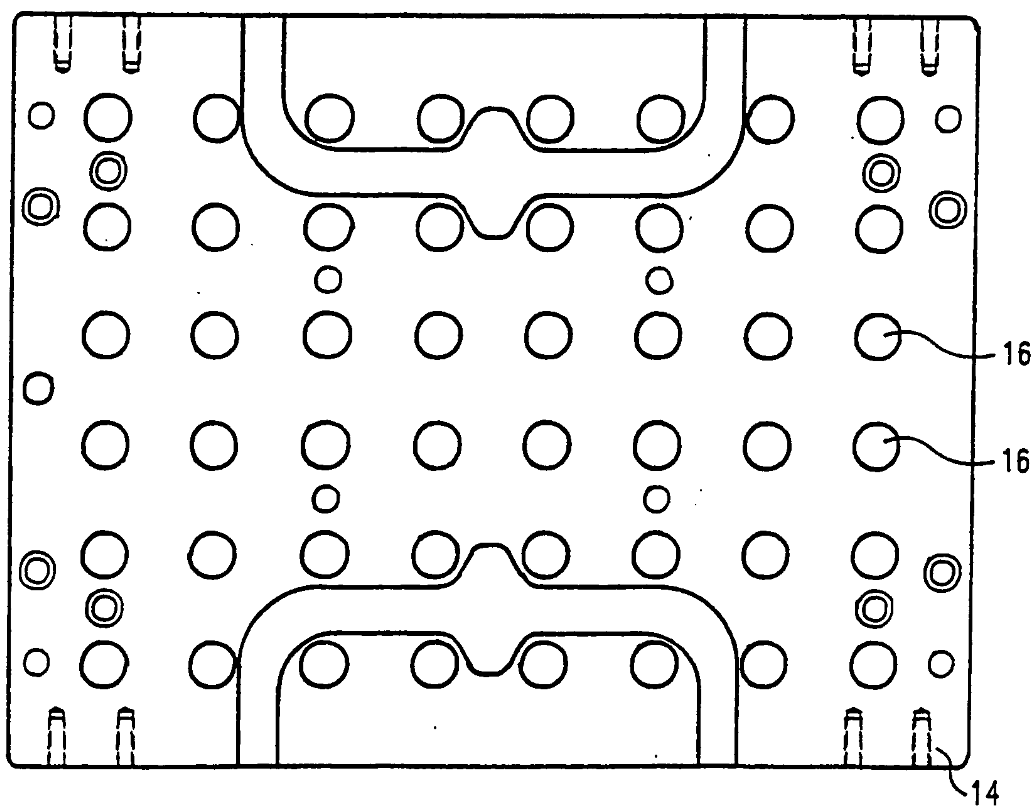


FIG. 9c

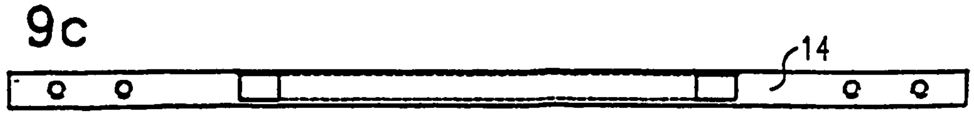


FIG. 10a

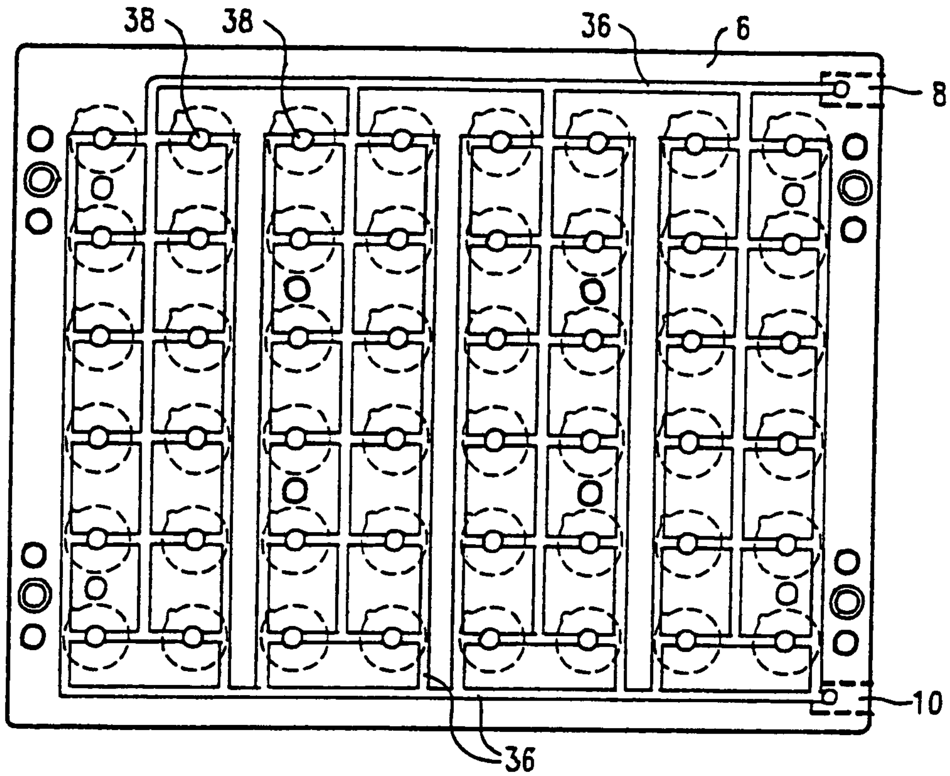


FIG. 10b

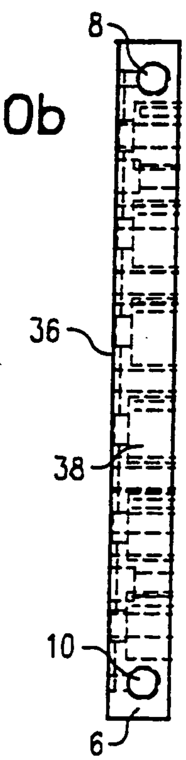


FIG. 10C

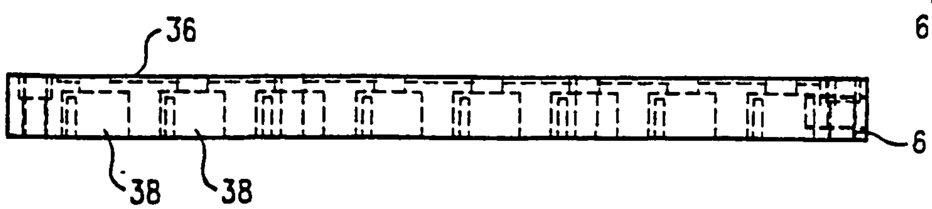
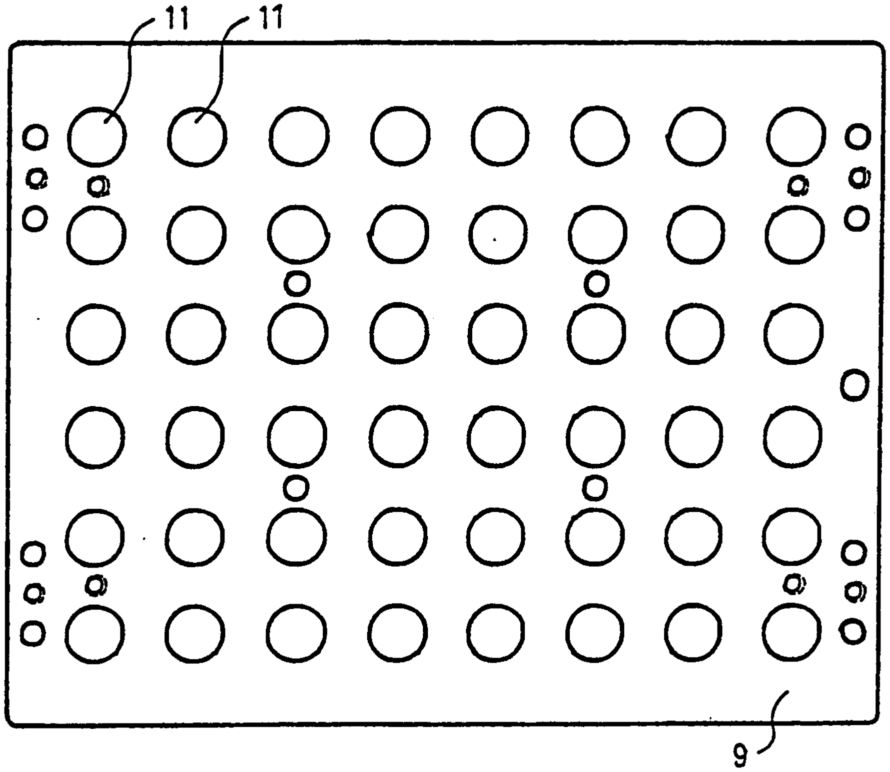


FIG. 11a



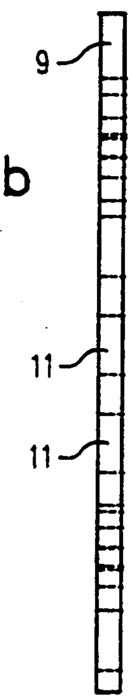


FIG. 11b

FIG. 11c

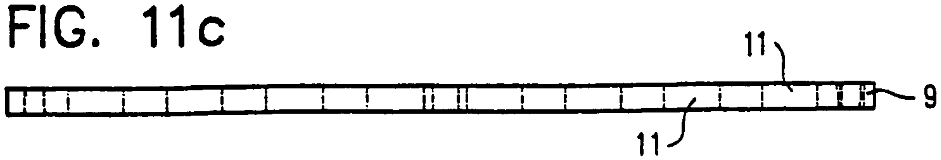


FIG. 12a

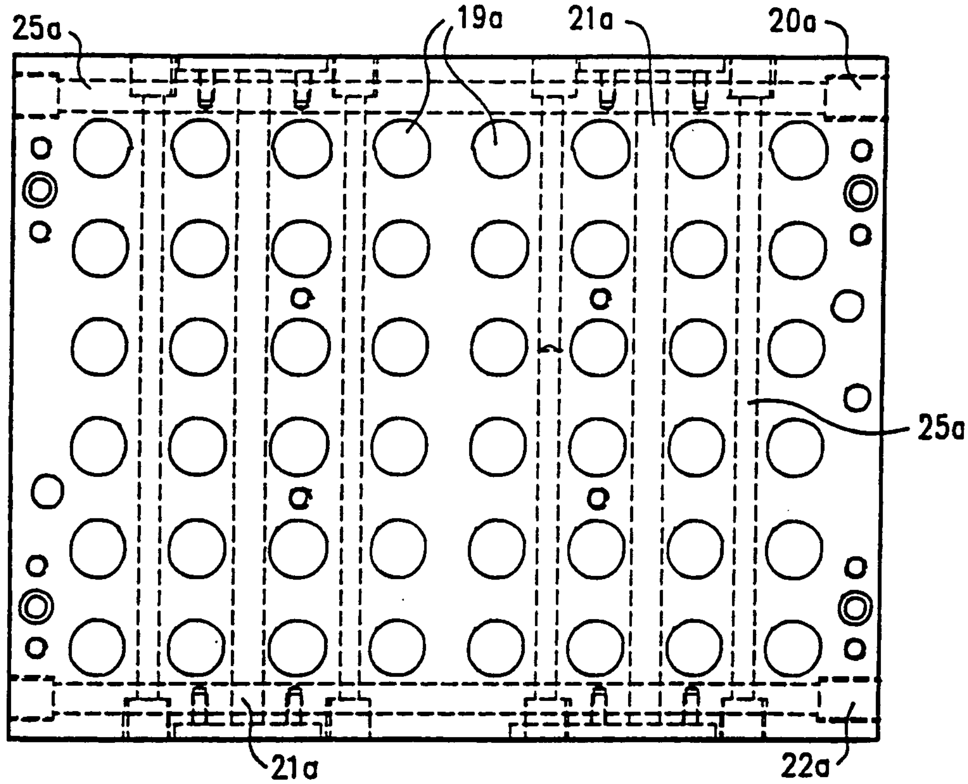


FIG. 12b

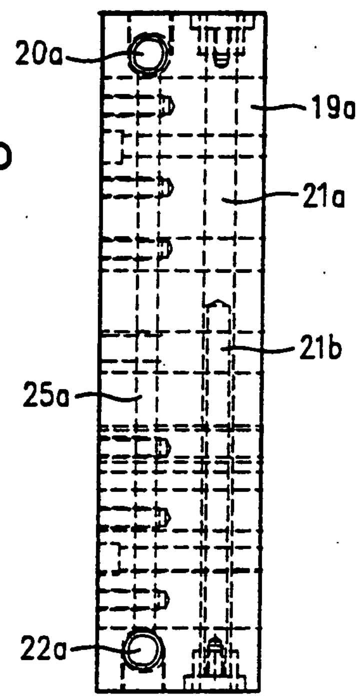


FIG. 12c

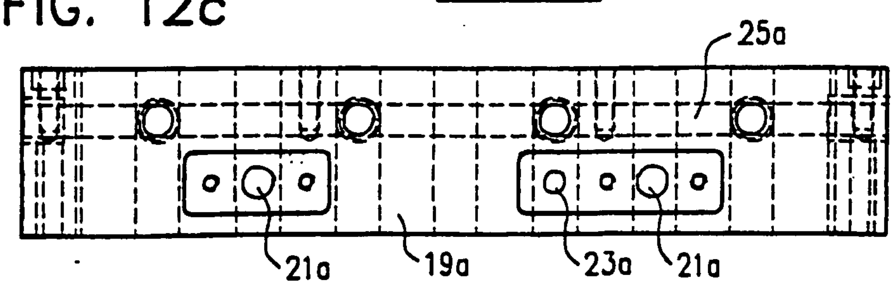


FIG. 13a

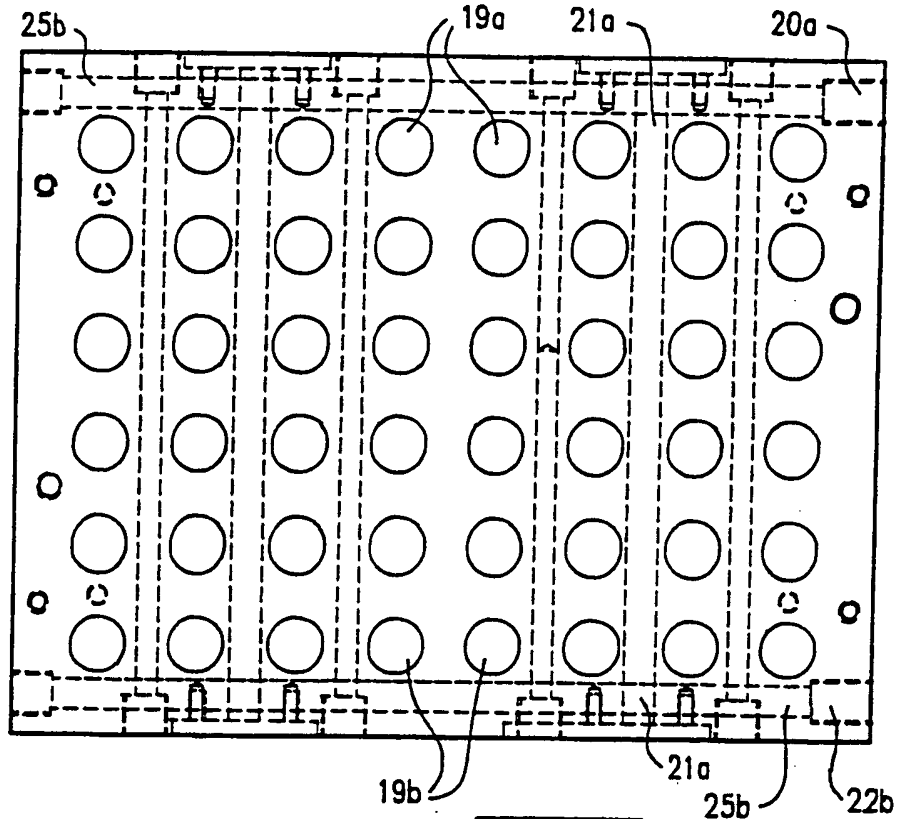


FIG. 13b

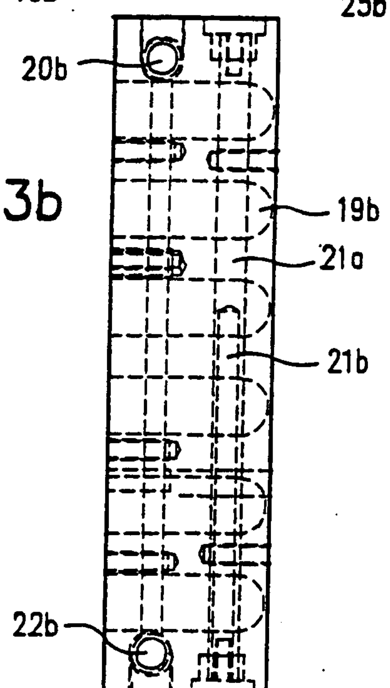


FIG. 13c

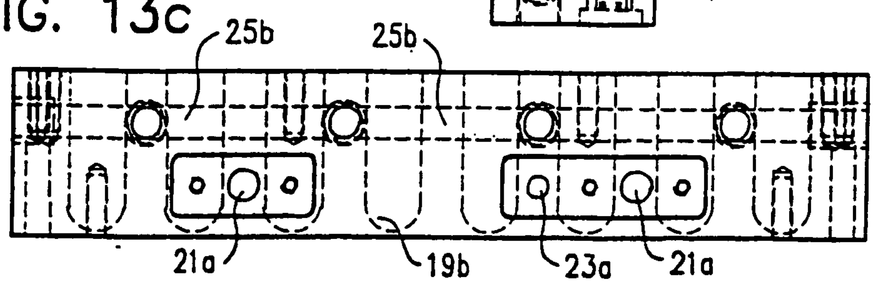


FIG. 14a

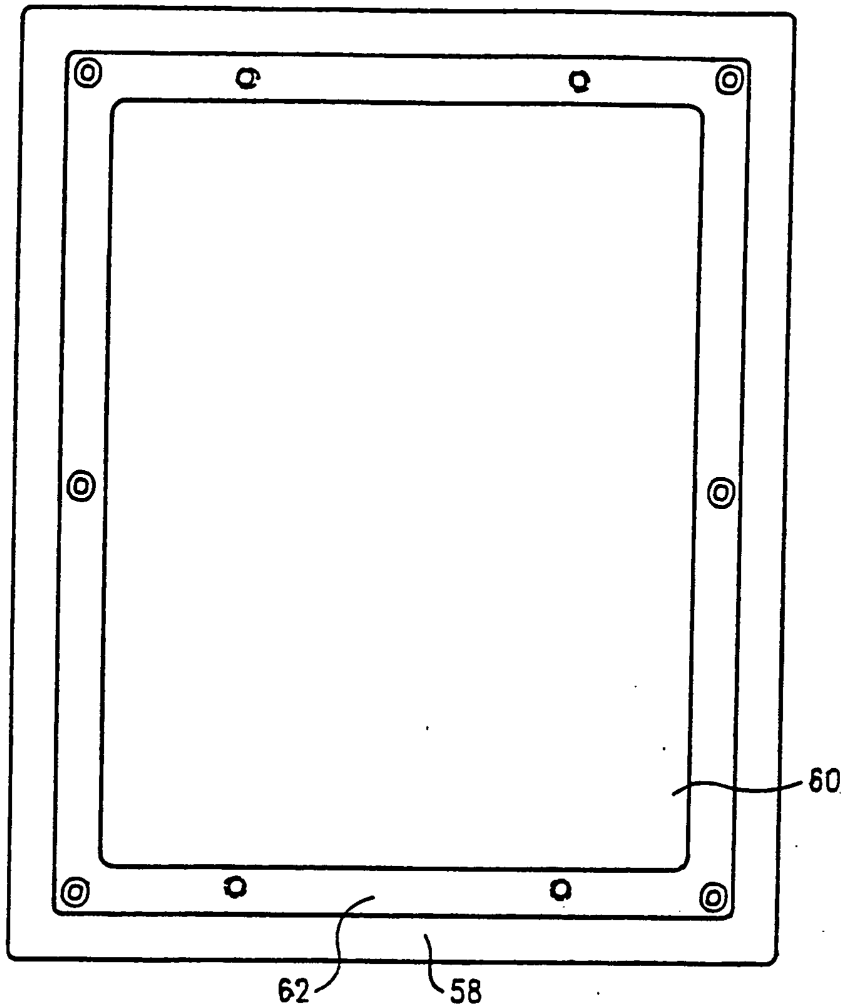


FIG. 14c

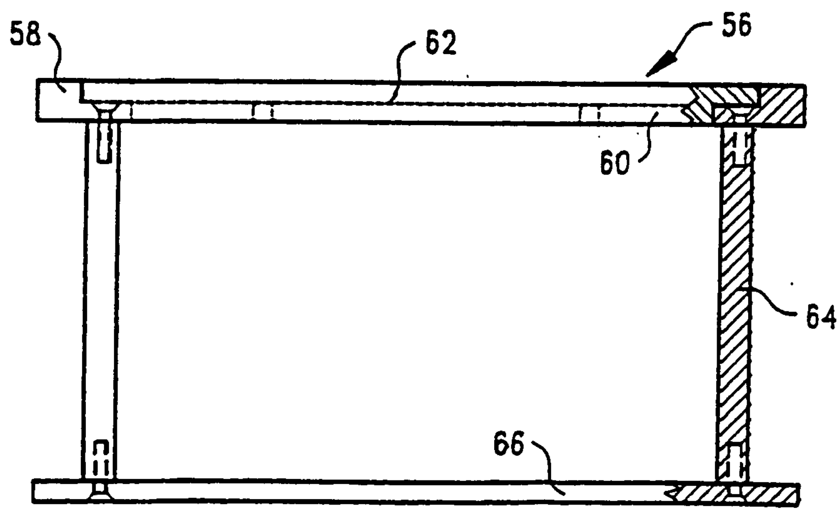
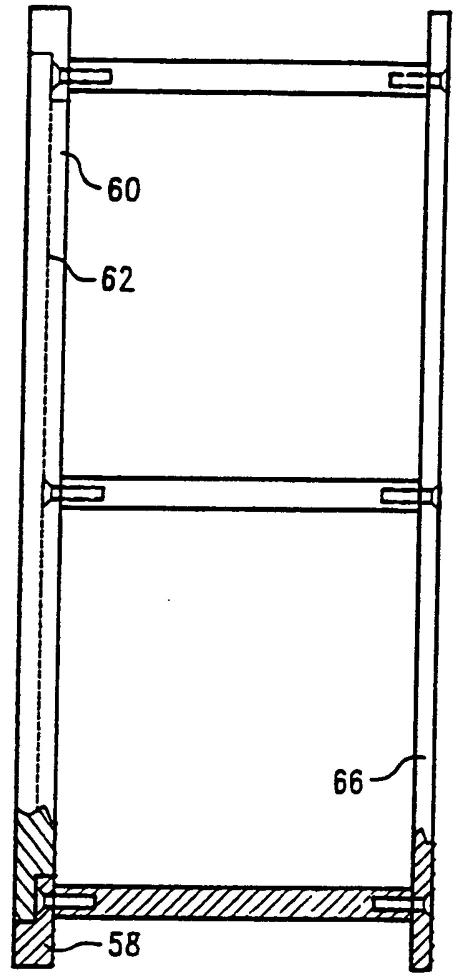


FIG. 14b



INTERNATIONAL SEARCH REPORT

International application N .
PCT/US96/14325

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C08F 2/00; G01N 21/00; B01L 3/00; C12C 1/00
US CL : 422/131, 81, 99, 102; 435/303.1, 305.1, 305.2, 305.3
According to International Patent Classification (IPC) r to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/131, 81, 99, 102, 297; 435/303.1, 305.1, 305.2, 305.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic dat base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 5,219,528 (CLARK) 15 June 1993, figure 1.	1 -- 2-47
Y,P	US, A, 5,472,672 (BRENNAN) 05 December 1995, figure 1, column 8.	2-47
Y	US, A, 5,324,483 (CODY ET AL) 28 June 1994, column 10.	4-47
Y	US, A, 4,625,096 (FLETCHER) 25 November 1986, column 1.	6-9
A	US, A, 5,354,663 (CHARM ET AL) 11 October 1994, entire document.	1-47
A	US, A, 5,053,454 (JUDD) 01 October 1991, entire document.	1-47

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the internati nal search 20 NOVEMBER 1996	Date of mailing f the international search report 24 DEC 1996
Name and mailing address f the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile N . (703) 305-3230	Authorized officer Kelley Thomas for CHRISTOPHER KIM Telephon No. (703) 308-0651

INTERNATIONAL SEARCH REPORT

International application N .
PCT/US96/14325

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation f document, with indication, where appropriate, of the relevant passages	Relevant to claim N .
A	US, A, 4,526,690 (KIOVSKY ET AL) 02 July 1985, entire document.	1-47
A	US, A, 4,493,815 (FERNWOOD ET AL) 15 January 1985, see entire document.	1-47
A	SYRO II MULTIPLE SYNTHESIS ROBOT brochure.	1-47